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Renal Insufficiency Is a Component of COACH Syndrome

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Two sisters, ages 23 years and 6 years, respectively, were found to have congenital ataxia, bilateral coloboma, mental retardation and abnormal liver function. Magnetic resonance imaging showed cerebellar vermis hypoplasia in the younger girl and liver biopsy showed hepatic fibrosis in the older sister. This combination of findings suggested a diagnosis of COACH syndrome which is characterized by hypoplasia of cerebellar vermis, oligophrenia, congenital ataxia, coloboma, and hepatic fibrosis.

COACH syndrome is a newly recognized condition. So far, five cases have been reported from three sibships. We report two additional cases from one sibship and suggest that several other cases may already exist in literature that were not recognized as having COACH syndrome. The occurrence of multiple cases in single sibships suggests autosomal recessive inheritance. In addition to previously described findings typical of COACH syndrome, the older of our patients showed progressive renal insufficiency with fibrocystic changes on renal biopsy. Renal function has not been described consistently in previous reports of COACH syndrome but has been abnormal in all cases in which it has been investigated. We suggest that renal insufficiency should be considered a common manifestation of COACH syndrome.

KEY WORDS: COACH syndrome, hepatic fibrosis, fibrocystic renal disease, mental retardation, vermis hypoplasia, coloboma, ataxia, nephronophthisis

INTRODUCTION

COACH syndrome is a syndrome characterized by hypoplasia of **C**erebellar vermis, **O**ligophrenia, congenital **A**taxia, **C**oloboma and **H**epatic fibrosis; it was first described in 1989 in three patients from two sibships [Verloes and Lambotte, 1989]. Wiesner et al. reported on two more siblings in an abstract [Wiesner et al., 1992]. We now report on two sisters who appear to have all manifestations of COACH syndrome to emphasize renal involvement in this condition and to increase the clinical awareness of this newly recognized syndrome.

CLINICAL REPORTS

The patients are two sisters now 23 and 6 years old, respectively, born of apparently healthy, nonconsanguineous parents. The father's sister and paternal grandmother were reported to have had polycystic kidneys but the father himself had not been tested. The mother was 21 years old at the time of birth of patient 1 and 38 years old at the time of the birth of patient 2. The father was 23 years old at the time of the birth of patient 1 and 40 years old at the time of birth of patient 2. The patients are two of five sibs. The other three are healthy and include a female, 20 years old and two males, 17 and 12 years, respectively.

Patient 1

Patient 1 was born after a 39-week normal gestation characterized by a weight gain of 15 kg and normal fetal activity; she was delivered by use of outlet forceps. Birth weight was 3.17 kg. There were no problems at birth but psychomotor development was delayed. She was able to sit at 1 year, stand at 2 years, walk at 4.5 years and speak at 5.5 years. Height was 155 cm at age 17 (20th centile) and 163 cm at age 21 (40th centile). Weight was 33.4 kg at age 17 and 41.3 kg at age 21 (both below 5th centile). Visual difficulty was noted during the first year of age. Visual acuity at age 21 was 20/200 in each eye. The patient lived at home, attended special educational classes and was at the 5th grade level at age 21. She had no seizures. Menarche occurred at age 16 and periods were scanty but regular. Hepatosplenomegaly was noted at age 21. Portal hypertension, esophageal varices, and abnormal renal function were discovered at age 22 when she presented with hematemesis and melena; a transjugular intrahepatic portosystemic shunt was placed.

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On examination at age 23 years, this was a slender young woman with a height of 165 cm, weight of 41 kg, and blood pressure of 120/80 mm Hg. She had midfacial hypoplasia, ocular hypertelorism, shallow orbits, pouty lower lip, prognathism, alobular pinnae, bilateral nystagmus and colobomas of both optic nerves. Cranium was normal. Lungs were clear. Heart sounds were normal. There were no murmurs. Hepatosplenomegaly was present. There was no ascites. She was hypotonic and had hyperextension at metacarpophalangeal joints. Gait was ataxic.

Laboratory results included: Hb, 11.9 g/dl; Hct, 35%; white cells, 2,800/μl; platelets, 67,000/μl; sodium, 144 mmol/l; potassium, 4.4 mmol/l; chloride, 116 mmol/l; CO_2, 15 mmol/l; glucose, 95 mg/dl; blood urea nitrogen, 66 mg/dl; creatinine, 2.6 mg/dl; uric acid, 6.7 mg/dl; total protein, 5.7 g/dl; albumin, 2.9 g/dl; calcium, 8.7 mg/dl; phosphorus, 3.5 mg/dl; magnesium, 1.8 mg/dl; total bilirubin, 0.6 mg/dl; triglycerides, 187 mg/dl; cholesterol, 152 mg/dl; lactate dehydrogenase, 147 u/l (normal); alkaline phosphatase, 289 u/l (normal, 38–126 u/l); creatine phosphokinase, 97 u/l (normal); aspartate aminotransferase, 53 u/l (normal, 7–40 u/l); glutamyl aminotransferase, 110 u/l (normal, 7–40 u/l); and gamma-glutamyl aminotransferase, 181 u/l (normal, 8–78 u/l). These results were consistent with chronic liver disease, hypersplenism and chronic renal insufficiency. A liver biopsy (Fig. 1) documented extensive fibrotic bands altering the liver architecture and separating the liver parenchyma into lobules that retained the central veins. The fibrosis extended between the portal triads, and the bile ducts in the areas of fibrosis were hypertrophied but not dilated. There was an inflammatory infiltrate in the portal triads. The portal arteries and veins were normal and there was no vasculitis. Urinalysis showed pH of 5.0 (simultaneous plasma CO_2 was 15 mmol/l), specific gravity 1.010, trace protein, trace blood, normal urobilinogen, and no glucose, ketones or nitrite. Urine microscopy showed occasional red and white cells but no casts. Urine protein was 447 mg per 24 hours. After bicarbonate supplementation, serum bicarbonate rose to 22 mmol/l and urine pH rose to 7.0 consistent with a diagnosis of proximal renal tubular acidosis. Voiding cystourethrogram was normal. There was no vesico-ureteric reflux. A renal biopsy (Fig. 2) showed microcystic disease and interstitial fibrosis. Out of a total of 13 glomeruli, 5 were sclerosed, 5 were normal, and 3 showed subcapsular fibrosis, shrunken glomerular tufts and wrinkled capillary basement membranes. Several tubules were atrophic or cystically dilated. The interstitium ranged from normal to areas of fibrosis with focal mild mononuclear infiltrate. The arterioles showed some hyalinization. Plasma levels of very long chain fatty acids and phytanic acid were measured by capillary gas chromatography of fatty methyl esters. Both very long chain fatty acids and phytanic acid levels were essentially normal.

Patient 2

Patient 2 was born after a 37-week normal gestation and was delivered normally after induced labor. Birth weight was 3 kg and length was 50 cm. Psychomotor development was delayed. She was able to sit at 1 year, stand at 2 years, walk at 4.5 years, and started speaking at 4 years. At 5 months of age, height was 58 cm and weight was 4.5 kg (both below 5th centile). Visual difficulty was noted during the first year of age. Visual acuity was 20/80 in each eye at age 3. She had no seizures. Hepatomegaly and abnormal liver function tests were found at age 5.

At age 6, she was a small girl; height was 88 cm (below 5th centile), weight was 15 kg (below 5th centile, and blood pressure was 80 mm Hg systolic. Cranium was normal. Face showed midfacial hypoplasia, ocular hypertelorism, shallow orbits, "pouty" lower lip, alobular pinnae, left ptosis, nystagmus, and medial and inferior deviation of the left eye. Ophthalmoscopy demonstrated colobomas of both optic nerves and dysplasia of the right optic nerve. Lungs were clear. Heart sounds were normal. There were no murmurs. The abdomen

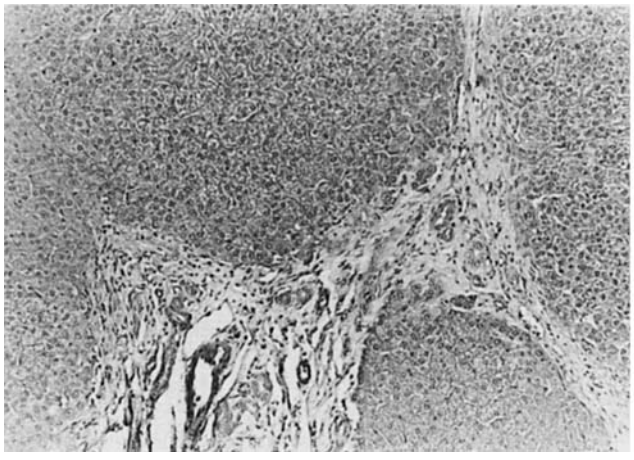

Fig. 1. Liver biopsy from patient 1. The hepatic lobules are separated by widened fibrous septa connecting the portal regions. Proliferating bile ducts are also seen in the areas of fibrosis. Original magnification, 100×.

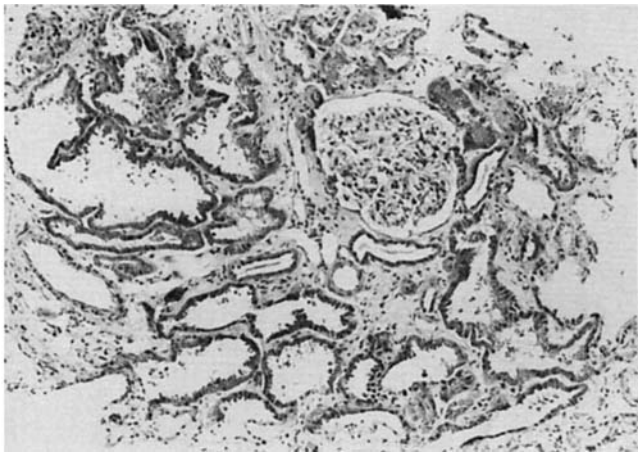

Fig. 2. Kidney biopsy from patient 1. Renal tubules are dilated and the intervening interstitium shows moderate widening due to fibrosis. The single glomerulus seen in this section is well preserved. Original magnification, 100×.

was protuberant. Hepatomegaly was present. The spleen was not palpable. There was no ascites. She had generalized hypotonia and there was hyperextension at the metacarpophalangeal joints. Gait was slightly ataxic.

Results of laboratory examinations included: Hb, 11.8 g/dl; Hct, 35%; white cells, 12,200/μl; platelets, 346,000/μl; sodium, 141 mmol/l; potassium, 4.1 mmol/l; chloride, 104 mmol/l; bicarbonate, 23 mmol/l; glucose, 117 mg/dl; blood urea nitrogen, 19 mg/dl; creatinine, 0.4 mg/dl; uric acid, 4.9 mg/dl; total protein, 7.4 g/dl; albumin, 4.0 g/dl; calcium, 9.3 mg/dl; phosphorus, 4.4 mg/dl; total bilirubin, 0.6 mg/dl; conjugated bilirubin, 0.12 mg/dl; triglycerides, 120 mg/dl; cholesterol, 268 mg/dl; lactate dehydrogenase, 309 u/l (normal for 6 years); alkaline phosphatase, 731 u/l (normal for 6 years, 150–420 u/l); creatine phosphokinase, 71 u/l (normal for 6 years); aspartate aminotransferase, 131 u/l (normal, 15–60 u/l); glutamyl aminotransferase, 333 u/l (normal, 7–40 u/l); and gamma-glutamyl aminotransferase, 286 u/l (normal, 7–33 u/l). These results are consistent with hepatocellular damage. Urinalysis showed pH, 5.0; specific gravity, 1.020; and a negative reaction for protein, blood, glucose, bile, ketones and nitrite. Urine microscopy revealed 0–2 white cells per high power field but no red cells or casts. A magnetic resonance imaging scan of the brain (Fig. 3) showed that the cerebellar vermis was absent. There was no connection of the cerebellum to the spinal cord inferiorly. The fourth ventricle was abnormally displaced superiorly. The aqueduct was normal. There were no signs of hydrocephalus. Frontal lobes were prominent. The corpus callosum was thin.

DISCUSSION

We report on the sixth and seventh patients with COACH syndrome. These patients are very similar to those described in the previous two reports on this condition. However, renal status was not well studied in previous reports. Of the three patients described by Verloes and Lambotte [1989], one was reported to have had proximal renal tubular acidosis and mild elevation of blood urea nitrogen level; renal function was not reported in the other two. One patient had a kidney biopsy but it yielded an inadequate specimen. Of the two patients reported in abstract form by Wiesner et al. [1992], renal findings are mentioned in one who had multiple small medullary cysts. In our first patient, renal insufficiency was discovered at age 21 years and a renal biopsy showed fibrocystic changes. The second patient has normal renal function at age 6 years. Nine years before the acronym COACH syndrome was coined, Dieterich and Straub [1980] described two sisters with "familial juvenile nephronophthisis with hepatic fibrosis and neurocutaneous dysplasia" who had all the characteristics of this condition, including the fibrocystic disease in the kidneys. Verloes and Lambotte [1989] did not include these patients in their COACH syndrome description because of the nephronophthisis, especially since renal abnormalities were not recognized as a prominent feature of COACH syndrome at that time. The syndrome of nephronophthisis can be difficult to differentiate with certainty from other causes of tubulocystic change in the kidneys because there is no single clinical or histological feature of nephronophthisis that is completely specific. Cohen and Hoyer [1986] have suggested that early and prominent thickening of tubular basement membrane might be a somewhat specific feature of nephronophthisis but the tubular basement membrane is also nonspecifically thickened in the areas of tubular atrophy that are commonly present in nephronophthisis and in other tubulocystic diseases of the kidney. Although Dieterich and Straub [1980] labeled their patients as having nephronophthisis, their report does not make a specific comment regarding tubular basement membrane thickening. In our patients, there was moderate thickening of tubular basement membranes in atrophic tubules but not in the tubules that were preserved. Overall, it is likely that the renal condition in our patients is similar to that in the patients of Dieterich and Straub [1980], and that slowly progressive renal insufficiency is a frequent manifestation in COACH syndrome.

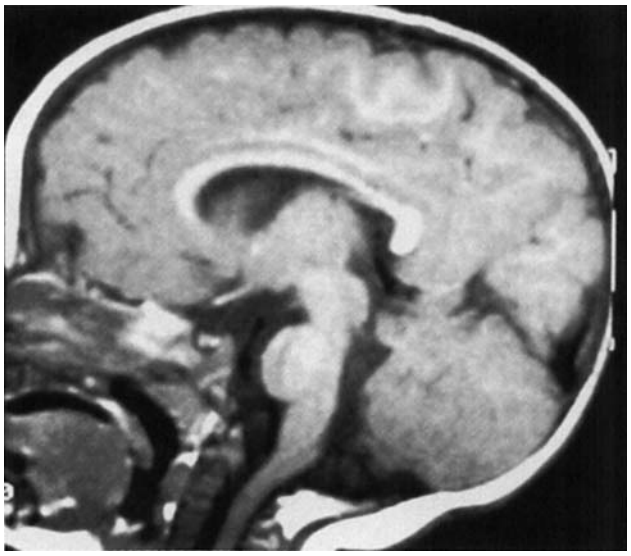

Fig. 3. Magnetic resonance imaging scan from patient 2. The cerebellar vermis is absent. Prepontine and basilar cisterns are large. The fourth ventricle is displaced but there is no hydrocephalus. The aqueduct is normal.

Several other conditions have partial clinical similarity to COACH syndrome and can be considered in its differential diagnosis (Table I). Joubert syndrome was initially described [Joubert et al., 1969] as a syndrome of aplasia of the cerebellar vermis with episodic hyperpnea, abnormal movements of the eyes and tongue, ataxia, and mental retardation. Subsequently, a number of associations have been described, individually or together, for Joubert's syndrome (reviewed in Saraiva and Baraitser [1992]), including coloboma [Lindhout et al., 1980; Laverda et al., 1984], retinal dystrophy [Tomita et al., 1979; King et al., 1984], renal cysts [Ivarsson et al., 1993], and hepatic fibrosis [Lewis et al., 1994]. It is difficult to be entirely certain that COACH syndrome is an entity separate from Joubert's syndrome, but the absence of hyperpnea, and of abnormal movements of the eyes and tongue in COACH syndrome indicate that they are likely separate conditions.

TABLE I. Comparison of COACH Syndrome With Related Syndromes

	Cerebellar v. hypoplasia	Psychomotor retardation	Coloboma	Hepatic fibrosis	Fibrocystic kidneys	Other
COACH	+	+	+	+	+	
Dieterich and Straub [1980]	+	+	+	+	+	
Joubert et al. [1969]	+	+	±	±	±	Hyperpnea, abnormal movements of tongue
Hunter et al. [1974] and Thompson & Baraitser [1986]	+	+	+	+	+	Characteristic facies
Dekaban [1969]	+	+	−	−	+	Optic atrophy
Matsuzaka et al. [1986]	+	+	−	+	+	Optic atrophy
Labrune et al. [1990]	−	+	−	+	+	
Wakakura et al. [1993]	+	+	−	?	+	Optic atrophy, adult onset, heart block, sensorineural deafness, no ataxia

Hunter et al. [1974] described two sibs with liver fibrosis, renal cysts, choroidal coloboma and indirect evidence of cerebellar and vermis dysfunction (nystagmus, ataxia, and infantile tachypnea). These patients also had athetoid spasticity and characteristic facies (anteverted noses and carp mouth, reminiscent of Smith-Lemli-Opitz syndrome [Smith et al., 1967]. Subsequently, Thompson and Baraitser [1986] described two more sibs with similar features. Verloes and Lambotte [1989] in their original description of COACH syndrome excluded these patients because: (a) at that time cystic change in the kidneys was not recognized as a feature of COACH syndrome, and (b) the patients appeared to have different facies. Dekaban [1969] described two siblings with Leber optic atrophy [Leber, 1867], and immaturity of cerebral neurons, hypoplasia of the cerebellar vermis and fibrocystic renal disease. One, on whom autopsy was performed, also had fatty liver, patent foramen ovale, and heterotypic gastric mucosa in the esophagus. Subsequently, eight patients were described in four reports from Japan (reviewed in Matsuzaka et al. [1986]) with a similar syndrome that in addition included hepatic fibrosis but not coloboma. These patients were different from the narrow description of COACH syndrome in that they did not have coloboma. Labrune et al. [1990] described a boy with congenital hepatic fibrosis, polycystic kidneys, mental retardation and abnormal facial appearance who was different from COACH syndrome in that he did not have vermis hyperplasia or coloboma. Wakakura et al. [1993] described an adult patient with retinal degeneration, optic atrophy, microcystic renal disease, and vermis hypoplasia. Liver function tests were mildly abnormal but a liver biopsy was not performed. Colobomas were not present and there was no ataxia. The patient also had heart block, sensorineural deafness, glucose intolerance and hyperlipidemia. At this time, it is difficult to be entirely certain that these conditions do not represent different points along the spectrum of a common condition that includes COACH syndrome as one of its manifestations.

The occurrence of multiple affected patients in single sibships, and the fact that both parents of our patients are healthy, indicate that this condition is likely to be inherited as an autosomal recessive condition. The basic defect underlying COACH syndrome is not known. Lewis et al. [1994] have suggested that the basic defect in COACH syndrome, Joubert syndrome and other similar conditions might be a disturbance in normal epitheliomesenchymal interactions, where different mutations might lead to overlapping but different clinical manifestations. No specific molecular defect has yet been identified. In view of the clinical involvement of brain, liver and kidneys, we examined the possibility that this is a peroxisomal disorder. The normal plasma levels of very long chain fatty acids and of phytanic acid argue against the presence of the common peroxisomal disorders, including Zellweger syndrome, adrenoleukodystrophy, Refsum disease, rhizomelic chondrodysplasia punctata and hyperpipecolic acidemia. More studies are needed to define the biochemical basis of COACH syndrome.

In conclusion, we suggest that COACH syndrome may be the same condition as described in earlier reports by Dieterich and Straub [1980], and possibly by Hunter et al. [1974], and by Thompson and Baraitser [1986]; that it is unlikely to be a peroxisomal disorder; and that progressive renal insufficiency should be considered a common finding of this syndrome.

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